

INCREASED FREQUENCY OF GENETIC THROMBOPHILIA
IN WOMEN WITH COMPLICATIONS OF PREGNANCYMICHAEL J. KUPFERMINC, M.D., AMIRAM ELDOR, M.D., NITZAN STEINMAN, M.D., ARIEL MANY, M.D.,
AMIRAM BAR-AM, M.D., ARIEL JAFFA, M.D., GIDEON FAIT, M.D., AND JOSEPH B. LESSING, M.D.**ABSTRACT**

Background Obstetrical complications such as severe preeclampsia, abruptio placentae, fetal growth retardation, and stillbirth are associated with intervillosus or spiral-artery thrombosis and inadequate placental perfusion. Whether these complications are associated with an increased frequency of thrombophilic mutations is not known.

Methods We studied 110 women who had one of the above-mentioned obstetrical complications and 110 women who had one or more normal pregnancies. The women were tested several days after delivery for the mutation of adenine to guanine at nucleotide 506 in the factor V gene (factor V Leiden), the mutation of cytosine to thymine at nucleotide 677 in the gene encoding methylenetetrahydrofolate reductase, and the mutation of guanine to adenine at nucleotide 20210 in the prothrombin gene. Two to three months after delivery the women were tested for deficiency of protein C, protein S, or antithrombin III and for the presence of anticardiolipin antibodies.

Results The mutation at nucleotide 506 in the factor V gene was detected in 22 of the women with obstetrical complications and in 7 of the women with normal pregnancies (20 percent and 6 percent, respectively; $P=0.003$). Twenty-four women with complications, as compared with nine women without complications, were homozygous for the C677T mutation in the gene encoding methylenetetrahydrofolate reductase (22 percent and 8 percent, respectively; $P=0.005$). The G20210A mutation in the prothrombin gene was found in 11 women with complications as compared with 3 women without complications (10 percent and 3 percent, respectively; $P=0.03$). Overall, 57 women with obstetrical complications had a thrombophilic mutation, as compared with 19 women with normal pregnancies (52 percent and 17 percent, respectively; $P<0.001$). Deficiency of protein S, protein C, or antithrombin III or anticardiolipin antibodies were detected in an additional 14 women with complications, as compared with 1 woman with a normal pregnancy (13 percent and 1 percent, respectively; $P<0.001$).

Conclusions Women with serious obstetrical complications have an increased incidence of mutations predisposing them to thrombosis and other inherited and acquired forms of thrombophilia. (N Engl J Med 1999;340:9-13.)

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SEVERE preeclampsia, abruptio placentae, fetal growth retardation, and stillbirth contribute greatly to maternal and fetal morbidity and mortality. Their causes are unknown, but all of them may be associated with abnormal placental vasculature and disturbances of hemostasis, leading to inadequate maternal-fetal circulation.¹⁻⁷

Several thrombophilic mutations are associated with an increased risk of thromboembolic complications. Resistance to activated protein C caused by an adenine-to-guanine mutation at nucleotide 506 in the factor V gene (the factor V Leiden mutation) has been linked with an increased risk of venous thromboembolism.⁸⁻¹⁰ Homozygosity for the mutation of cytosine to thymine at nucleotide 677 in the gene encoding methylenetetrahydrofolate reductase results in decreased synthesis of 5-methyltetrahydrofolate, the primary methyl donor in the conversion of homocysteine to methionine, and the resulting increase in plasma homocysteine concentrations is a risk factor for venous and arterial thrombosis.^{11,12} A recently described guanine-to-adenine mutation at nucleotide 20210 in the prothrombin gene is associated with higher plasma concentrations of prothrombin and an increased risk of venous thromboembolism,¹³ myocardial infarction,¹⁴ and cerebral-vein thrombosis.¹⁵

We hypothesized that the mutations predisposing patients to thrombosis may be important risk factors for obstetrical complications that are related to inadequate maternal-fetal circulation. We therefore studied the relation between severe preeclampsia, abruptio placentae, fetal growth retardation, and stillbirth, on the one hand, and several thrombophilic mutations, on the other. We also searched for deficiency of protein S, protein C, or antithrombin III and for the presence of anticardiolipin antibodies and lupus anticoagulant, which are also associated with thrombophilia.

METHODS**Study Subjects**

Between September 1996 and November 1997, we studied 110 consecutive women who had pregnancies complicated by severe preeclampsia, abruptio placentae, fetal growth retardation, or stillbirth. Severe preeclampsia was defined by a blood pressure

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higher than 160/110 mm Hg; urinary protein excretion greater than 5 g per 24 hours; a platelet count of less than 100,000 per cubic millimeter; the combination of hemolysis, high serum aminotransferase concentrations, and a platelet count below 100,000 per cubic millimeter; or eclampsia.¹⁶ Abruptio placentae was diagnosed on the basis of clinical criteria, and only women with grade 2 or 3 abruption (abruption associated with vaginal bleeding or concealed hemorrhage; uterine tenderness; and fetal distress, maternal shock, or maternal coagulopathy) were included.⁶ Fetal growth retardation was defined by a birth weight below the 5th percentile for gestational age, according to the criteria of Brenner et al.¹⁷ The exclusion criteria for women whose pregnancies were complicated by fetal growth retardation were the presence of congenital malformations or chromosomal abnormalities in the fetus, recent cytomegalovirus infection (defined by the presence of IgM anticytomegalovirus antibodies or increasing titers of IgG anticytomegalovirus antibodies in paired blood samples obtained three to four weeks apart, as well as cytomegalovirus in the urine of the newborn), or drug or alcohol abuse during pregnancy. Stillbirth was defined as fetal death after 23 weeks' gestation. Exclusion criteria in cases of stillbirth were abnormal results of karyotyping of the stillborn fetus or congenital anomalies detected at autopsy, Venereal Disease Research Laboratory results positive for syphilis, positive tests for antibodies against red-cell antigens, recent cytomegalovirus infection, positive cultures for *Listeria monocytogenes* in samples from the fetus and placenta, and abnormal results on the oral glucose-tolerance test.

Women who had more than one complication during pregnancy (for example, severe preeclampsia and fetal growth retardation) were assigned to one of the four groups according to the following hierarchy: severe preeclampsia was considered the most important complication, followed by abruptio placentae, fetal growth retardation, and then stillbirth.

We also studied 110 women who had normal pregnancies and no history of thromboembolic complications during any pregnancy. Each of these women was matched for age and for the geographic origin of each parent with a woman with normal pregnancy. All the women were of Jewish origin and were classified as Ashkenazi, non-Ashkenazi, or mixed Ashkenazi and non-Ashkenazi according to their family origin. The study was approved by the ethics committee of the Tel Aviv Sourasky Medical Center, and informed consent was obtained from each woman. The women in both groups were enrolled while in the hospital after delivery.

At enrollment, blood was drawn from all the women for DNA analysis for thrombophilic mutations. Investigation of women whose pregnancies were complicated by fetal growth retardation or stillbirth was initiated at that time (e.g., a cytomegalovirus test and autopsy of stillborn infants were performed). The women were then asked to return at least two months after the delivery, at which time blood was drawn for the assessment of protein S, protein C, antithrombin III, anticardiolipin antibodies, and lupus anticoagulant. All the women had received prenatal care, which is covered by the health insurance mandated by law for all the citizens of Israel.

Molecular Diagnosis

Molecular diagnosis of the factor V Leiden mutation was performed as described by Brenner et al.¹⁸ The mutation in the methylenetetrahydrofolate reductase gene was detected as described by Frosst et al.¹¹ The mutation in the prothrombin gene was detected with use of a slight modification of the method of Poort et al.¹³ The forward primer was 5'CAACCGCTGGTATCAATGG3', and the reverse primer was as reported by Poort et al.¹³ This method yielded a DNA fragment of 253 base pairs, which was digested with *Hind*III.

Assays

Free protein S in plasma was measured with a specific enzyme-linked immunosorbent assay (Asserachrom free protein S assay, Diagnostica Stago, Asnières, France). Levels of protein C antigen and antithrombin III antigen were determined by rocket elec-

troimmunoassay with rabbit antihuman protein C (Sigma, Rehovot, Israel) and rabbit antihuman antithrombin III (Diagnostica Stago), respectively. The antithrombin III activity in plasma was determined by a chromogenic assay (Dade Diagnostica, Munich, Germany). Levels of IgG and IgM anticardiolipin antibodies were determined with an enzyme-linked immunosorbent assay (OR-GenTec, Mainz, Germany); measurement of more than 15 IgG phospholipid units was considered to be a positive result. The presence of lupus anticoagulant was determined as described elsewhere.¹⁹ For all these assays, the intraassay and interassay coefficients of variation were less than 6 percent.

Statistical Analysis

Results for the two groups were compared with use of two-tailed Student's *t*-tests, Fisher's exact tests, and Pearson's chi-square tests. Odds ratios and 95 percent confidence intervals were calculated. Statistical analyses were performed with the Statistical Package for the Social Sciences for Windows, version 6 (SPSS, Chicago).

RESULTS

The characteristics of the women with obstetrical complications and those with normal pregnancies are shown in Table 1. The gestational ages at delivery and the birth weight of the infants were significantly lower and the number of primiparous women was significantly higher in the group with complications. Of the 18 multiparous women with complications, 12 had had obstetrical complications in a previous pregnancy, 3 had had one normal pregnancy and one complicated pregnancy, and 3 had had normal pregnancies.

Thirty-four of the 110 women with complications (31 percent) had severe preeclampsia, indicated by a blood pressure higher than 160/110 mm Hg in 26 women; urinary protein excretion in excess of 5 g per 24 hours in 2; a platelet count below 100,000 per cubic millimeter in 2; the combination of hemolysis, high serum aminotransferase concentrations, and a platelet count below 100,000 per cubic millimeter in 3; and eclampsia in 1. Twenty women with complications (18 percent) had abruptio placentae, of whom three also had mild preeclampsia and seven had antepartum or postpartum hypertension. Eleven of the neonates in this group had birth weights below the 10th percentile for gestational age.¹⁷ Forty-four women (40 percent) had fetuses with growth retardation; 15 of these 44 women had mild hypertension (blood pressure elevated but not greater than 150/100 mm Hg). Twelve women (11 percent) had stillbirths. Two of these women had mild hypertension.

Overall, 57 of the 110 women with obstetrical complications (52 percent) had at least one of the three thrombophilic mutations, as compared with 19 of the 110 women with normal pregnancies (17 percent; odds ratio, 5.2; 95 percent confidence interval, 2.8 to 9.6) (Table 2). In addition, 14 other women in the group with complications (13 percent) had other types of inherited or acquired thrombophilia, as compared with only 1 woman in the group without complications (1 percent; odds ratio, 15.9; 95 percent confidence interval, 2.0 to 123.1). Seven

TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY WOMEN.*

CHARACTERISTIC	WOMEN WITH COMPLICATIONS (N=110)	WOMEN WITH NORMAL PREGNANCIES (N=110)	P VALUE
Age (yr)	29±6	28±5	0.6
Ethnic group (no.)			
Ashkenazi	48	48	1.0
Non-Ashkenazi	58	58	
Mixed†	4	4	
Smoker (%)	16	17	0.7
Week of gestation at delivery	32.2±4.7	39.5±1.4	<0.001
Infant's birth weight (g)	1375±693	3406±402	<0.001
Primiparity (no.)	92	62	<0.001

*Plus-minus values are means ±SD.

†Women of mixed ethnicity were those with one Ashkenazi parent and one non-Ashkenazi parent.

of the women with complications had protein S deficiency, one had protein C deficiency, and one had antithrombin III deficiency, whereas among the women with normal pregnancies, one had protein S deficiency and none were deficient in protein C or antithrombin III. Lupus anticoagulant was detected in one of five women with complications in whom the test for anticardiolipin antibodies was positive and in

none of the women with uncomplicated pregnancies. The combined prevalence of all the inherited and acquired types of thrombophilia in the women with obstetrical complications was 65 percent, as compared with 18 percent in the women without complications (odds ratio, 8.2; 95 percent confidence interval, 4.4 to 15.3) (Table 2).

Five women with complications and one woman with a normal pregnancy had multiple thrombophilic mutations (Table 2). Combinations of other types of thrombophilia were found in another five women in the study group and in none of the women with normal pregnancies. Each of the women with combined thrombophilia was considered only once in the statistical analysis.

The odds ratios for the prevalence of thrombophilic mutations in the women with obstetrical complications as compared with the women without complications are shown in Table 3. The prevalence of the three mutations was 53 percent among the women with severe preeclampsia, 60 percent among those with abruptio placentae, 50 percent for women who had fetuses with growth retardation, and 42 percent for women who had stillbirths. The prevalence of all the types of inherited and acquired thrombophilia that we studied was 68 percent in women with severe preeclampsia, 70 percent in women with abruptio placentae, 61 percent in women

TABLE 2. PREVALENCE OF INHERITED AND ACQUIRED THROMBOPHILIA IN THE STUDY WOMEN.*

TYPE OF THROMBOPHILIA	THROMBOPHILIA AMONG WOMEN WITH COMPLICATIONS (N=110)	THROMBOPHILIA AMONG WOMEN WITH NORMAL PREGNANCIES (N=110)	ODDS RATIO (95% CI)	P VALUE
	no. (%)			
Inherited				
Factor V Leiden mutation, ++ or +/-†	22 (20)	7 (6)	3.7 (1.5-9.0)	0.003
Methylenetetrahydrofolate reductase mutation, ++	24 (22)	9 (8)	3.1 (1.4-7.1)	0.005
Prothrombin mutation, +/-	11 (10)	3 (3)	3.9 (1.1-14.6)	0.03
Total	57 (52)	19 (17)	5.2 (2.8-9.6)	<0.001
Acquired or inherited				
Deficiency of protein S, protein C, or antithrombin III	9 (8)	1 (1)	9.7 (1.2-78.0)	0.01
Presence of anticardiolipin antibodies	5 (5)	0	2.0 (1.7-2.3)	0.02
Deficiency of protein S, protein C, or antithrombin III or presence of anticardiolipin antibodies	14 (13)	1 (1)	15.9 (2.0-123.1)	<0.001
All types	71 (65)	20 (18)	8.2 (4.4-15.3)	<0.001

*CI denotes confidence interval, ++ homozygous, and +/- heterozygous. Combined thrombophilias among the women with complications were as follows: factor V Leiden ++ and the methylenetetrahydrofolate reductase mutation ++ (one patient), factor V Leiden +/- and the methylenetetrahydrofolate reductase mutation ++ (four), factor V Leiden +/- and anticardiolipin antibodies (one), the methylenetetrahydrofolate reductase mutation ++ and protein C deficiency (one), protein S deficiency and anticardiolipin antibodies (two), and anticardiolipin antibodies and lupus anticoagulant (one). Among the women with normal pregnancies, one had a combined prothrombin mutation +/- and factor V Leiden +/-.

†Among the women with complications, 2 were homozygous and 20 were heterozygous for factor V Leiden; all 7 with this mutation who had normal pregnancies were heterozygous.

TABLE 3. PREVALENCE OF INHERITED THROMBOPHILIAS IN WOMEN WITH SPECIFIC OBSTETRICAL COMPLICATIONS, AS COMPARED WITH WOMEN WITH NORMAL PREGNANCIES.*

GENOTYPE	SEVERE PREECLAMPSIA (N=34)		ABRUPTIO PLACENTAE (N=20)		FETAL GROWTH RETARDATION (N=44)		STILLBIRTH (N=12)	
	NO. WITH THROMBO- PHILIA	ODDS RATIO (95% CI)	NO. WITH THROMBO- PHILIA	ODDS RATIO (95% CI)	NO. WITH THROMBO- PHILIA	ODDS RATIO (95% CI)	NO. WITH THROMBO- PHILIA	ODD RATIO (95% CI)
Factor V Leiden mutation, +/+ or +/-	9	5.3 (1.8–15.6)	5	4.9 (1.4–17.4)	5	1.9 (0.6–6.3)	3	4.9 (1.1–22.3)
Methylenetetrahydrofolate reductase mutation, +/+	7	2.9 (1.0–8.5)	3	2.0 (0.5–8.1)	12	4.2 (1.6–10.9)	2	2.2 (0.4–11.8)
Prothrombin mutation, +/-	2	2.2 (0.4–13.9)	4	8.9 (1.8–43.6)	5	4.6 (1.0–20.0)	0	0
Total	18	5.4 (2.3–12.4)	12	7.2 (2.6–20.0)	22	4.8 (2.2–10.3)	5	3.4 (1.0–11.9)

*CI denotes confidence interval, +/+ homozygous, and +/- heterozygous.

whose fetuses had growth retardation, and 58 percent in women who had stillbirths.

The 23 women with severe preeclampsia and thrombophilia delivered infants at an earlier mean (\pm SD) gestational age and with a lower mean birth weight than the 11 women with severe preeclampsia and no thrombophilia (gestational age, 31.7 ± 3.8 vs. 35.1 ± 3.6 weeks; $P=0.03$; birth weight, 1375 ± 684 vs. 1975 ± 504 g; $P=0.01$). There were no differences in these variables between the women with and those without thrombophilia in the other three subgroups (those with abruptio placentae, fetal growth retardation, or stillbirth).

Of the 15 multiparous women with obstetrical complications who had also had complications during previous pregnancies, thrombophilia was found in 10 (67 percent).

DISCUSSION

In this case-control study, we found a high prevalence (52 percent) of mutations in the genes encoding factor V, methylenetetrahydrofolate reductase, and prothrombin in otherwise healthy women who had severe complications of pregnancy. The incidence of these mutations in women with normal pregnancies who were matched with the women with complications for age and the geographic origin of each parent was only 17 percent. This study included only women who had severe obstetrical complications associated with abnormalities in the maternal-fetal circulation, and none of the women had a history of a previous thromboembolic event.

The factor V Leiden mutation was detected in 20 percent of the women with obstetrical complications, as compared with 6 percent of the women without complications. The rate of 6 percent is similar to the reported incidence of this mutation in healthy white people²⁰ and in the Israeli population.²¹ This mutation was significantly more prevalent in women with severe preeclampsia, abruptio placentae, or stillbirth

than in the women with uncomplicated pregnancies. In previous studies, resistance to activated protein C was detected in 16 percent²² and the factor V Leiden mutation in 9 to 22 percent²³⁻²⁵ of women with preeclampsia. In two of these studies, the prevalence of the mutation was significantly greater in women with preeclampsia than in women without complications.^{23,24} Of the women with abruptio placentae or stillbirth, 25 percent had the factor V Leiden mutation. In two other studies of women who delivered stillborn infants, 17 percent and 49 percent had the factor V Leiden mutation.^{19,26} In our study, 11 percent of women with fetuses affected by growth retardation had the factor V Leiden mutation, a prevalence that did not differ significantly from that among women with normal pregnancies; these findings confirm an earlier report.²⁷ The factor V Leiden mutation was recently found to be associated with a reduction in the risk of intrapartum bleeding, conferring a possible survival advantage in carriers of this mutation.²⁷

Homozygosity for the mutation in the methylenetetrahydrofolate reductase gene was found in 22 percent of the women with obstetrical complications, as compared with 8 percent of the women with normal pregnancies. This 8 percent prevalence is similar to that reported for the Israeli population²¹ and other groups.^{11,28,29} An increase in homozygosity for the methylenetetrahydrofolate reductase mutation associated with preeclampsia was reported in Italy²⁴ and Japan.³⁰ Hyperhomocysteinemia was found in 31 percent of women with abruptio placentae or placental infarction, as compared with 9 percent of a control group ($P<0.05$).³¹

The recently described mutation in the prothrombin gene is associated with an increased risk of venous and arterial thromboembolism.^{13,14} We found the prevalence of this mutation to be 10 percent in the group with complications, as compared with 3 percent in the group without complications. The latter value is similar to that found in a study of 474

normal subjects (2 percent).¹³ The prothrombin mutation was significantly more frequent in women with abruptio placentae and fetal growth retardation, but not in those with severe preeclampsia.

Fourteen women with obstetrical complications had other types of inherited or acquired thrombophilia, which were diagnosed at least two months after delivery. The most frequent abnormality was protein S deficiency (seven women), which was found most often in women who had stillbirths (17 percent), as previously reported by others.^{26,32}

Altogether, 65 percent of the women with complications had some form of inherited or acquired thrombophilia, as compared with 18 percent of the women with normal pregnancies. The presence of these abnormalities in association with hypercoagulability further supports the proposed relation between impaired placental development and perfusion and abnormal hemostasis. The known thrombotic features of placental vascular lesions and the increased risk of thrombosis associated with the presence of thrombophilia strongly suggest a cause-and-effect relation between these inherited and acquired anomalies and serious obstetrical complications.

In conclusion, our findings suggest that women with severe complications of pregnancy should be tested for markers of thrombophilia, even in the absence of a history of thromboembolism. Because these complications tend to recur^{6,32,33} (for instance, preeclampsia recurs at a rate of 20 percent³³), the presence of thrombophilia in these women may be an important consideration in planning future pregnancies. Although it is not known whether complications of pregnancy are more likely to recur in women with thrombophilia, the high rate of recurrence found in the 15 multiparous women in our study who had obstetrical complications in previous pregnancies suggests that this possibility should be evaluated further.

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CORRECTION

Increased Frequency of Genetic Thrombophilia in Women with Complications of Pregnancy

Increased Frequency of Genetic Thrombophilia in Women with Complications of Pregnancy . On page 9, on lines 12 and 13, factor V Leiden should have been identified as "the mutation of *guanine to adenine at nucleotide 1691*," not "the mutation of *adenine to guanine at nucleotide 506*," as printed. The Results section of the abstract should have started, "The mutation at *nucleotide 1691*," not "The mutation at *nucleotide 506*," as printed. Also on page 9, in the right-hand column, the sentence that begins on line 10 should have read, "Resistance to activated protein C caused by a *guanine-to-adenine mutation at nucleotide 1691*," not "caused by an *adenine-to-guanine mutation at nucleotide 506*," as printed.